Distinct child-to-adult BMI trajectories are associated with different levels of adult cardiometabolic risk.

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ABSTRACT

Aims: The relationship between life-course body mass index (BMI) trajectories and adult risk for cardiovascular disease (CVD) is poorly described. In a well-characterized longitudinal cohort, we aimed to identify BMI trajectories from early childhood to adulthood and investigate their association with CVD risk factors (type 2 diabetes mellitus (T2DM), high-risk lipid levels, hypertension, and high carotid intima-media thickness (cIMT)) in adulthood (34 - 49 years).

Methods and results: Six discrete long-term BMI trajectories were identified using Latent Class Growth Mixture Modelling among 2631 Cardiovascular Risk in Young Finns Study participants (6 to 49 years): stable normal (55.2%), resolving (1.6%), progressively overweight (33.4%), progressively obese (4.2%), rapidly overweight/obese (4.3%), and persistent increasing overweight/obese (1.2%). Trajectories of worsening or persisting obesity were generally associated with increased risk of CVD outcomes in adulthood (24-49 years) (all risk ratios, RRs, >15, p-values <0.05 compared with the stable normal group). Although residual risk for adult T2DM could not be confirmed (RR=2.6, CI=0.14–8.23), participants who resolved their elevated child BMI had similar risk for dyslipidemia and hypertension as those never obese or overweight (all RRs close to 1). However, they had significantly higher risk for increased cIMT (RR=3.37, CI=1.80–6.39).

Conclusion: long-term BMI trajectories that reach or persist at high levels associate with CVD risk factors in adulthood. Stabilizing BMI in obese adults and resolving elevated child BMI by adulthood might limit and reduce adverse cardiometabolic

profiles. However, efforts to prevent child obesity might be most effective to reduce the risk for adult atherosclerosis.

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Introduction

The prevalence of overweight and obesity has increased substantially in both adults and children[1, 2]. These trends are predicted to plateau in developed countries[3], or to keep increasing globally, with a projected 1.35 billion overweight and 573 million obese adults by 2030[4]. Child adiposity is associated with adverse long-term cardiovascular disease (CVD) risk[2, 5-7]. To date, epidemiologic studies examining associations between obesity and adult CVD risk have focused on body mass index (BMI) from a single or limited number of time-points[6, 8, 9], ignoring the dynamic changes in BMI that occur over time and the potential diversity in child-to-adult BMI developmental patterns.

Newer statistical techniques allow the investigation of the heterogeneity of BMI trajectories that might exist[10-12]. A number of studies have prospectively explored BMI trajectories in the periods of childhood, crossing over adolescence, using raw BMI or BMI z-scores[10, 13-15], but none have covered a period long enough to encompass the life-course from young childhood until mid-adulthood. As a result, the progression of BMI from childhood into adulthood is less well-described[16]. Recent data suggest obese individuals who become non-obese between childhood and adulthood have a normalization of adult CVD risk[8]. However, it is unknown if the shape of BMI developmental patterns across the life-course, and in particular whether different patterns of high BMI incidence/resolution or stabilization from childhood to adulthood, play any role in predicting CVD risk in mid-adulthood. Determining if the development or resolution of abnormal BMI status at different ages predicts subsequent CVD risk might help inform public policy and interventions.

Using data from the 31-year prospective Cardiovascular Risk in Young Finns Study (YFS), we aimed to identify subgroups of participants who share similar trajectories in BMI from childhood though mid-adulthood, and determine the independent association of these BMI trajectories with adult CVD outcomes.

Methods

Study sample

Detailed descriptions of the YFS have been published previously[17-19]. This study considers a subset of 2631 YFS participants (1208 males, 1423 females) whose height and weight were measured on at least 3 occasions between 1980 and 2011. The minimum of 3 measures per participant included the initial childhood measure (1980), the last available BMI measure at any of the adult follow-ups (2001, 2007, or 2011), as well as one BMI measure between baseline and the last available BMI measure. BMI at each follow-up was calculated as $Weight\ (kg)/Height(m)^2$. Participants were aged 6-18 years in 1980 and 34-49 years at the latest follow-up in 2011. On average, participants had 5.4 individual BMI records (71% had ≥5). BMI measures were not utilized if participants were currently pregnant. Participants or their parents provided written informed consent, and the study was approved by the Ethics Committee of the Hospital District of Southwest Finland.

Definition of adult CVD outcomes

Adult CVD risk outcomes of type 2 diabetes mellitus (T2DM), hypertension, and high-risk lipid levels were assessed in 2001, 2007, and 2011, whereas high-risk carotid intima-media thickness (cIMT) was assessed in 2001 and 2007. CVD outcomes at the latest available examination were considered using standard cut-offs.[8] A detailed description of the definition and the prevalence of each dichotomous outcome among the study sample, and the number of participants treated with lipid-lowering-, blood-pressure-lowering and diabetes medications in adulthood is presented in Methods S1.

Statistical Methods

Latent BMI trajectories identification

Heterogeneity in the longitudinal development of BMI was investigated using Latent Class Growth Mixture Modelling (LCGMM) to identify subgroups of YFS participants who shared similar underlying BMI trajectories between age 6 and 49 years. A series of LCGMM considering several polynomial specifications of BMI as a function of age and a number of variance-covariance structures for the random-effects were fit using the `lcmm` package in `R`[20].

The choice of the best model was based on different indices of goodness of fit and discrimination (Bayesian information Criteria (BIC), log-likelihood, proportion of subjects classified in each class with a posterior probability >0.7, and values of mean posterior class membership probabilities) as well as clinical plausibility[20-22]. The online supplement provides full details on the strategies used for model building, including specification of functional form and variance-covariance structure of the model, identification of the optimal number of distinct latent classes, and the computation and analyses of post-fit indices (Methods S2).

Association of BMI trajectory groups with adult CVD outcomes

To determine the association between trajectory groups and the different CVD risk factor outcomes in adulthood, the trajectory group memberships identified by LCGMM were introduced as predictors of each adult outcome in Poisson regression models with robust error variance. This method was chosen over logistic regression since the prevalence was larger than 10% for 5 out of 6 adult outcomes, and effect measures were thus reported in terms of relative risks rather than in odd ratios[23-25].

For a subset of 2421 participants (1073 males) who had all 6 CVD outcomes in adulthood, we constructed a combined cardiovascular load risk-score (range 0-6), calculated as the arithmetic sum of the number of adverse CVD outcomes at the latest adult follow-up (Table S1). The association between the BMI trajectory groups with the combined CVD risk load variable (classified as 0, 1, ≥2) was assessed using ordinal logistic regression. The adjusted models included year of birth and sex as covariates.

Results

Latent BMI trajectories

Using BIC, class membership posterior probabilities and classification to assess the goodness-of-fit of the competing LGCMM models (Methods S2, Table S2), we identified 6 discrete life-course BMI trajectories among the 2631 YFS participants (Fig 1, Fig 2). 55.2% followed a trajectory where the average predicted BMI levels remained within normal weight status throughout follow-up ('stable normal' group, class 1, N=1453), 33.4% followed a trajectory of increasing BMI that led to overweight from the mid 30s ('progressively overweight' group, class 3, N=879), 4.2% had BMI levels increasing rapidly from childhood, resulting in an overweight status in early adulthood and worsening obesity by early mid-adulthood ('progressively obese' group, class 4, N=110), 4.3% were borderline overweight in early childhood (age 6 years), overweight in mid-childhood (age 12 years) and obese but stabilizing by age 20 years ('rapidly overweight/obese group', class 5, N=113), 1.2% followed a trajectory of persistent and increasing obesity throughout their observed life-course, leading to BMI levels ≥40 kg/m^2 in mid-adulthood ('persistent increasing overweight/obese', class 6, N=33), and 1.6% were overweight or obese in childhood increasing to obese by 25 years but progressively reversed their elevated BMI status between 30 and 50 years of age ('resolving' group, class 2, N=43). Although some of the identified latent classes had low percentages of participants (<6%), they were highly discriminated with high mean a posteriori probabilities and high posterior probabilities (Table S2, Methods S2). Table S3 provides parameter estimates of the fixed and random components of the 6-class quadratic mixture model. The considered age range was represented in all 6 classes, but there were differences in the average age across follow-ups, as well as the mean age at baseline. Sex

differences were noted in specific classes of trajectories. Females were over-represented in the 'stable normal' trajectory group, but the 'progressively overweight' (class 3) and 'rapidly overweight/obese' (class 5) groups, contained more males (Table 1). The 'progressively obese', 'persistent increasing overweight /obese' and 'resolving' groups (classes 4, 6, and 2) had more females.

Association of BMI trajectory groups with adult CVD outcomes

The proportion of adult T2DM, hypertension, high-risk low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, and cIMT in the considered sample is shown in Table 2. Compared with participants classified in the 'stable normal' class (class 1), all BMI classes with worsening or persisting obesity (i.e. classes 3-6) had significantly higher risk for all considered adult outcomes. For those in the 'resolving' group (class 2, N=43), the estimated differences in risk were not consistent in direction across individual cardiometabolic traits. The risk ratio (RR) of hypertension, high-risk LDL-cholesterol and high-risk HDL-cholesterol were similar to those in class 1 (RRs close to 1), but the risk for T2DM was increased (RR=2.13, CI=0.14–8.23), and the risk for high-risk triglycerides was decreased slightly (RR=0.78, CI=0.09–2.4) (Table 2), although the confidence intervals for these estimates were too wide and included one. In contrast, participants in the resolving group (class 2) had nearly 3.5 times the risk for abnormal cIMT compared with participants in the normal stable BMI trajectory group (RR=3.37, CI=1.80–6.39, p-value<0.01, Table 2). Additional outcome, class specific results, and their interpretations are detailed in Table 3. Although the direction of effects remained similar, estimates for most outcomes attenuated towards the null after further adjustment for family history, adult socio-economic status, and adult

physical activity level (Table 2). In contrast, RRs below one (class 2) for hypertension and high-risk triglycerides outcomes became stronger upon adjustment, but confidence intervals included 1.

The probability of observing a non-null cumulative CVD risk load (i.e. having 1 or more CVD risk factor in adulthood) increased from 0.2 to 0.7 as BMI trajectory changed from 'stable normal' (class 1) to the 'persistent increasing overweight/obese' group (class 6) (Fig 3). The probability of having 2 or more CVD outcomes in adulthood was 11 times higher in the 'persistent increasing overweight/obese' group compared with the 'stable normal' group. The 'resolving' class was more likely than the 'progressively overweight' to maintain an ideal cardiometabolic profile (0.58 vs. 0.43 probability of having 0 outcomes).

Discussion

We investigated how distinct long-term BMI trajectories observed between 6 and 49 years of age influence later CVD risk. Our findings are consistent with previous studies showing that "excess BMI-years" increase risk of T2DM[16, 26] and CVD risk factor levels. Our observational data suggest that stabilizing BMI among obese adults could help limit their adverse CVD risk profiles and that reversing high BMI in young adulthood may lead to better cardiometabolic profiles than remaining stable overweight. Our results suggest that to effectively attenuate preclinical atherosclerosis risk, obesity prevention should ideally target children.

The more than doubled risk difference observed for adult T2DM in the resolving class compared to the normal stable class suggested a potential residual effect of child overweight/obesity on adult T2DM risk, even with resolution of BMI status later in life. However, because the confidence intervals for this estimate included the null, this finding needs to be confirmed in further studies with a larger number of resolvers. Our results suggest that the absence of BMI stabilization in adulthood, rather than the age of obesity onset, is strongly associated with adult T2DM, hypertension, and high-risk lipid levels. This is consistent with an observational study reporting the risk of T2DM was mainly associated with increased BMI levels close to the time of diagnosis[16]. In contrast, the cumulative burden of the number of life-years spent obese may be a stronger predictor of the adult risk of hypertension. Our findings also suggest that the mechanism by which excess BMI may increase circulating LDL-cholesterol and triglycerides is primarily immediate and that a longer exposure to obesity does not additionally increase the risk of developing abnormal lipids beyond the level of BMI attained. Although the direction of risk estimates was not consistent

across considered metabolic traits, these data suggest that completely reversing high BMI, even after childhood, is beneficial for most outcomes. However, this risk reduction was not observed for high cIMT.

For cIMT, the data suggest that elevated BMI status in early life may alter arterial structure in a way that is not reversible, and that the effect of youth overweight/obesity on the risk for adult pre-atherosclerosis may not be correctable, even when weight status is normalized later in life[1]. This finding is in accordance with recent clinical studies suggesting childhood obesity may initiate pathogenic processes in the arterial wall that persist even with later improvements in body weight[9, 27], and an observational study among male defense force recruits where elevated BMI at age 17 years was associated with later coronary heart disease, independent of adult BMI levels[16]. Taken together, these data are consistent with atherosclerosis development occurring across the life-course such that a longer history of relative overweight/obesity starting earlier in life contributes additional, residual risk unable to be reversed by weight correction later in life. In contrast, our findings contradict those reported in a recent longitudinal study where reductions in BMI category, even if not sustained throughout the life-course, were associated with decreased cIMT[28]. However, there were a number of differences between cohorts and approaches and compared with our study, the emphasis was on the effect of weight loss at any age in adulthood, rather than the effect of long-term developmental patterns of BMI.

Our data provides additional granularity of clinical importance to previous analyses from the YFS that suggested overcoming excess childhood adiposity by adulthood led to a normalization of all CVD risk outcomes in adulthood[8]. These analyses involved

subjective categorization of participants into four groups based on their movement between BMI status between two examinations (performed up to 31 years apart) in childhood and adulthood. In addition, 'true adiposity resolvers' (i.e. overweight or obese children who became normal weight adults), could not be distinguished from 'adiposity improvers' (i.e. overweight or obese children who became normal weight or overweight adults, respectively), or 'overweight persistent' (i.e. those overweight children who became overweight adults). Despite a high prevalence of adult overweight in our sample (reaching up to 36% overweight adults in 2011, Table S4), the previous approach collapsed 'overweight' and 'normal-weight' adults into a single category, preventing the discrimination of CVD risk between incident overweight and truly normative BMI trajectories. Therefore, it is possible the misclassification of participants in this group prevented detection of the residual effect of elevated childhood BMI on adult cIMT risk that we noted here[8].

Distinct life-course progressions of CVD risk factors have been shown to associate with subsequent CVD risk[29-31]. Consistent with our findings, recent studies suggest the cardiovascular consequences of obesity are cumulative, and that the duration of overweight or obesity may be a stronger predictor of CVD outcomes compared with a cruder measure of obesity-resolution or obesity-onset between two time-points[5, 32, 33]. Beyond the number of years spent living with an adverse weight status, the developmental period (childhood, puberty, mid-adulthood) at obesity onset, or the age at obesity resolution, may itself contribute to the strength of the association between change in BMI status and CVD outcomes[34, 35]. To overcome issues associated with discrete categorization of participants based on dichotomous measures of obesity or overweight at different ages[36, 37], a life-course perspective provides a useful avenue to

evaluate the impact of long-term BMI trajectory patterns on later-life CVD risk. Indeed, rather than modelling trajectories as individual deviation from population average age-BMI curves[11], identifying groups of individuals with similar patterns of BMI trajectories compliments individual-based approaches, as it can increase our understanding of how weight status fluctuations, and different pathways of obesity onset and development, impact subsequent CVD risk.

This study had several strengths. Our study includes a period large enough to examine the heterogeneity in BMI trajectories from childhood until mid-adulthood that allowed us to quantify adult CVD risk in groups of participants whose weight trajectories remained poorly described in previous studies.[10, 13-15]. In addition, the LCGMM approach used in this study allowed the *a-posteriori* identification of qualitatively distinct BMI trajectories in our data, thus overcoming misclassification and loss of information that can arise when defining groups of trajectories *a-priori*. Limitations included the lack of BMI observations in early childhood (<6 years) that precluded us from considering the critical period of adiposity rebound; the inclusion of a large racially-homogenous cohort of Northern European ancestry that could limit generalizability; and the lack of longitudinal measures on other indices of adiposity that might better reflect fat distribution and subcutaneous fat than BMI.

In conclusion, BMI trajectories from childhood to adulthood vary, with trajectories that reach or persist at high levels associated with an increased cumulative CVD risk load in mid-adulthood. The results for the individual cardiometabolic outcomes, however, are complex and not all consistent in direction. Our results suggest that the absence of BMI stabilization in adulthood may be a stronger determinant of adult

T2DM risk compared with the age at which obesity developed. In addition, the risk for adult hypertension was stronger among trajectory groups that developed high BMI early in life and were therefore obese for many years. Despite non-statistically significant estimates (probably attributable to small sample size), complete resolution of high-BMI appears to be associated with a normalization of risk for adverse lipid levels and hypertension in adulthood, although it is possible that some residual risk exists for T2DM. Together, the data suggests that resolving high adiposity even in young adulthood may be beneficial to long-term CVD risk. However, the markedly increased risk for high-risk cIMT in middle adulthood despite body weight normalization between childhood and adulthood emphasizes the potential importance of childhood obesity prevention to attenuate the risk of preclinical atherosclerosis.

Figure legends

Fig 1. Distinct latent body mass index (BMI) trajectories identified from childhood to adulthood in the Cardiovascular Risk in Young Finns Study from 6-49 years. Solid lines show class-specific mean predicted BMI levels as a function of age estimated from best fitting growth mixture model (6-class quadratic LGCMM). Dashed lines indicate estimated 95% confidence intervals, and shaded background areas indicate normal (green), overweight (blue), and obese BMI status (red) across the observed life-course (international childhood sex-specific cut points[38], were averaged across sex at each age to improve readability). Number of participants attributed to each latent class is shown in the legend.

Fig 2. Individual long-term body mass index (BMI) profiles within each identified latent trajectory class. Shown are the observed individual BMI profiles, colour-coded according to posterior BMI trajectory class membership (thin lines). Solid lines show the loess-smoothed BMI trajectories for the 6 identified latent classes (obtained by smoothing across all BMI profiles attributed to each latent class).

Fig 3. Predicted probability of having a cumulative cardiovascular disease (CVD) risk load of 0 (N=1360), 1 (N=540) and ≥2 (N=521) in the Cardiovascular Risk in Young Finns Study for each latent body mass index (BMI) trajectory class. The predicted probability plot is derived from the proportional odd ratios estimated for the sex- and adult age-adjusted ordinal logistic model.

Table 1. Participant characteristics for each of the six different latent body mass index trajectory groups

	Stable Normal	Resolving	Progressively overweight	Progressively obese	Rapidly overweight/obese	Persistent increasing overweight/obese	P-value*
	(class 1)	(class 2)	(class 3)	(class 4)	(class 5)	(class 6)	
	N=1453	N=43	N=879	N=110	N=113	N=33	
Mean age (sd) (years)	25.11 (12.8)	22.33 (12.6)	21.43 (12.0)	23.62 (12.7)	24.76 (12.5)	24.72 (12.5)	0.001
Min age–Max age (years)	6-49	6-49	6-49	6-49	6-49	6-49	1
Mean age baseline (sd) (years)	12.11 (4.2)	11.83 (4.0)	9.91 (3.8)	11.46 (4.0)	11.93 (3.9)	9.97 (3.6)	<0.001
Male, %	37.7	46.5	59.6	39	53.1	36.3	0.02

* p-values from Anova F-tests (comparisons of means) and from chi-square tests of independence (comparison of proportions).

sd = standard deviation.

Table 2. Sex and year of birth adjusted risk ratios (RR), 95% confidence intervals (CI), and Wald z-statistic p-values between body mass index (BMI) trajectory group and adult outcomes. Results of univariate models are presented in the first 3 columns, results in the greyed-out columns are those of models further adjusted for family history of each outcome, adult socio-economic status, and physical activity level in adulthood.

Outcome, Latent BMI trajectory group	**%**[f]	**RR**[c]	**95%CI**[c]	**P-value**	**RR**[c]	**95%CI**[c]	**P-value**
Type 2 diabetes	**3.5**						
Class 1[a]	1.4	1[b]	-	-	1	-	-
Class 2	2.6	2.13	0.14–8.23	0.31	1.93	0.11 – 9.73	0.40
Class 3	3.5	2.49	1.38–4.58	**0.002**	2.09	1.09 – 5.11	**0.02**
Class 4	17.1	13.05	6.71–25.17	**6.75×10^{-15}**	10.1	3.13 – 19.72	**0.03**
Class 5	12.6	9.33	4.39–19.08	**1.1×10^{-9}**	9.33	4.12 – 16.15	**0.002**

Class 6	20.1	19.45	8.63–31.16	**$7.5x10^{-10}$**	16.5	6.30 – 22.61	**0.01**
Hypertension[e]	**26.6**						
Class 1[a]	19.3	1	-		1	-	
Class 2	17.1	0.76	0.23–1.80	0.25	0.52	0.13 – 1.32	0.15
Class 3	26.9	1.64	1.36–1.99	**$2.3x10^{-9}$**	1.24	1.11 –1.99	**0.04**
Class 4	33.1	2.20	1.52–3.08	**$1.1x10^{-6}$**	2.12	1.15–2.89	**0.02**
Class 5	36.5	2.35	1.65–3.26	**$2.9x10^{-8}$**	2.28	1.32–3.02	**<0.01**
Class 6	40.6	3.18	1.77–5.35	**$1.6x10^{-5}$**	2.98	1.51–5.02	**0.03**
High-risk cIMT[e]	**13.1**						
Class 1[a]	7.8	1[b]	-		1	-	
Class 2	25.1	3.37	1.80–6.39	**$4.3x10^{-6}$**	3.12	1.51 –6.03	**0.04**
Class 3	13.3	1.70	1.30–2.22	**$4.1x10^{-3}$**	1.31	1.01–2.14	**<0.01**

Class 4	22.3	2.68	1.78–4.40	**$1.3x10^{-6}$**	2.19	1.31 –3.90	**<0.01**
Class 5	24.5	3.27	2.11–4.90	**$6.6x10^{-9}$**	3.10	1.92 –3.45	**0.02**
Class 6	25.8	3.49	2.32–5.71	**0.002**	3.14	2.21 –4.12	**<0.01**
High-risk LDL-C[e]	**15.2**						
Class 1[a]	9.4	1[b]	-	-	1[b]	-	-
Class 2	10.5	1.03	0.14–1.10	0.10	1.01	0.1 – 1.08	0.45
Class 3	16.5	1.47	1.16–1.84	**$3.5x10^{-5}$**	1.12	1.06 – 1.49	**0.02**
Class 4	17.9	1.59	1.37–1.95	**0.04**	1.30	1.17 – 2.57	**0.05**
Class 5	18.7	1.65	1.21–2.63	**0.006**	1.20	1.11 – 2.30	**0.03**
Class 6	19.8	1.78	1.11–2.72	**0.023**	1.51	1.05 – 2.94	**0.05**
High-risk HDL-C[e]	**24.4**						

Class 1[a]	11.4	1	-		1	-	
Class 2	14.6	1.07	0.72–1.19	0.16	1.03	0.22 – 1.11	0.36
Class 3	26.3	1.57	1.16–1.84	**$2.1 \times 10^{-11*}$**	1.24	1.12 –1.82	**0.03**
Class 4	41.8	1.75	1.04–12.1	**1.1×10^{-16}**	1.35	1.01–12.1	**<0.01**
Class 5	39.9	1.72	1.10–2.72	**1.9×10^{-9}**	1.41	1.02 –2.22	**<0.01**
Class 6	40.6	1.77	1.56–2.96	**2.45×10^{-3}**	1.37	1.26–2.60	**0.04**
High-risk triglycerides[e]	**12.5**						
Class 1[a]	4.8	1[b]	-		1	-	
Class 2	4.5	0.78	0.09–2.4	0.42	0.31	0.06 –2.12	0.42
Class 3	17.7	3.06	2.31–4.10	**2.1×10^{-15}**	2.89	2.02–4.08	**<0.01**
Class 4	27.7	5.62	3.61–8.53	**3.6×10^{-16}**	5.11	3.11 –9.58	**0.03**

Class 5	25.6	4.73	3.02–7.23	**4.3×10^{-15}**	4.24	3.02 –7.34	**0.02**
Class 6	18.9	4.03	1.56–8.56	**0.0001**	3.21	1.22 –9.60	**0.04**

[a]Latent BMI trajectory classes: Class 1, Stable normal trajectory (N=1453); Class 2, Resolving (N=43); Class 3, Progressively overweight (N=879); Class 4, Progressively obese (N=110); Class 5, Rapidly overweight/obese (N=113); and Class 6, Persistent increasing overweight/obese (N=33).

[b]Class1 is the reference group. Unadjusted models with only the trajectory groups were also fit but estimated RRs were not significantly different and the AIC suggested that the sex-and year of birth (YOB) adjusted models fit the data better (data not shown).

[c]for each latent class the RRs can be interpreted as the changes in relative ratios for belonging to a given class, vs. the reference class (here class 1). (i.e. a [RR] of 1.0, means there is no difference in risk between the trajectory group tested and the reference group. A RR of 0.5 means a 50% lower risk, and a RR of 1.5 means a 50% higher risk compared to reference.

[d]The 95%CI for the relative risks was obtained by log-likelihood profiling of the robust standard errors.

[e]Type 2 diabetes mellitus (T2DM) was defined as having fasting plasma glucose level of ≥7 mmol/l (126 mg/dl), or reporting the use of oral glucose-lowering medication or insulin but not reporting having type 1 diabetes, or receiving a diagnosis of T2DM from a physician at any of their adult follow-up examinations (2001, 2007, or 2011). Hypertension was defined as having a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg, or reporting the used of blood pressure–lowering medication. High-risk LDL-cholesterol was defined as having levels of ≥160 mg/dl (4.14 mmol/l) or reporting currently taking lipid-lowering medication. High-risk HDL-cholesterol was defined as having levels of <40 mg/dl (1.03 mmol/l). High-risk triglyceride was defined as having levels of ≥200 mg/dl (2.26 mmol/l) or higher[39]. High-risk cIMT was defined as cIMT values ≥90th percentile for age-, and sex-specific values.

[f]: Proportion of participants (%) with each adult outcome in the considered sample and within each trajectory class.

cIMT = carotid intima-media thickness; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Table 3. Additional class specific results and their interpretations for the considered adult outcomes.

Adult CVD outcome	Main result	Interpretation
T2DM	• Among obese adults, those whose BMI kept increasing in adulthood (classes 4 and 6) had greater risks of developing T2DM compared with those whose obesity developed sooner in life but stabilized in their early adulthood (class 5). (RR=1.4 (1.02-2.1) and RR=2.8 (1.2-4.3), respectively). • The 'progressively obese' group (class 4) and the 'persistent increasing overweight/obese' group (class 6) had the highest risks of T2DM, • The risk of T2DM for these participants (classes 4 and 6) are up to 7 times higher compared to participants in the 'Reversing' group (class 2) (RR=4.8 (1.1-20.8) and RR=7.3 (1.3-34.2), respectively), and those whose BMI stabilized to overweight levels (class 3)) (RR=5.2 (2.8-9.6) and RR=7.8 (2.8-14.2), respectively).	• Worsening obesity in adulthood increases risk for T2DM very significantly. • Reversing obesity or avoiding to become obese translates into a significant reduction or risk for adult T2DM.
High-cIMT	• Participants in the 'Resolving'group (class 2) still have nearly 3.5 times the risk for abnormal cIMT compared with participants who maintained a non-overweight/obese BMI from childhood to adulthood (class 1) (RR=3.37 (1.8-6.39).	• The effect of youth obesity on the risk for adult pre-atherosclerosis may not be reversible even with the normalization of high-BMI in later life.
Hypertension	• For hypertension, the risk ratios appeared smaller in the 'Resolving'group (class 2) compared with the incident overweight participants (class 3) (RR=0.59 (0.15-1.2), but were incremental in classes 4, 5 and 6 (RR=1.7 (1.2-2.4), RR=1.9 (1.4-2.6), and RR=2.5 (1.6-4.1), respectively).	• Resolving youth obesity may reduce risk of adult hypertension. • The number of years spent obese may be an important determinant of adult hypertension.
High-risk lipids	• The risk of raised adult LDL-C is similar in the 'Resolving' (class 2) and the 'stable normal' groups (class 1) (RR=1.03 (0.14-1.1), but ~1.5 higher in the incident overweight group (class 3) (RR=1.47 (1.16-1.84), Participants obese in adulthood (classes 4, 5 and 6) had close to twice the risk of developing abnormal LDL-C levels. (RR=1.6 (1.4-1.9), RR=1.7 (1.2-2.6), and RR=1.8 (1.1-2.7), respectively). • High triglycerides level was ~3 times more likely in the incident overweight group (class 3) compared with the normal stable group (class 1) (RR=3.06 (2.3-4.1)). The highest risk was for those who became obese in adulthood (class 4) (RR=5.6 (3.6-8.5)). • Participants who became overweight or obese had greater risks of having lower HDL-C levels in mid-adulthood, especially those with persisting and increasing obesity (class 6) (all RRs >1.5 for classes 3 to 6).	• A longer exposure to obesity may not additionally increase the risk of developing abnormal LDL-C, HDL-C and triglycerides levels (immediate effect of excess BMI)

BMI = body mass index; cIMT = carotid intima-media thickness; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RR = risk ratio; T2DM = type 2 diabetes mellitus.

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Availability of data and material

The dataset supporting the conclusions of this article were obtained from the Cardiovascular Risk in Young Finns study (YFS) after submission and approval of our study plan by the Young Finns Study coordinators. The YFS dataset comprises health related participant data and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these ethical restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case to case basis upon request only. Data requests should be addressed to the project coordinator, Dr. Olli Raitakari (Email:olli.raitakari@utu.fi), Tel: +358-2-333-7220 Fax: +358-2-333-7270. Written requests should be sent to: Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Kiinamyllynkatu 10, FIN-20520 Turku, FINLAND.